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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,262	04/05/2005	Masahiko Koike	084437-0172	4696

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EXAMINER	
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ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,262	KOIKE ET AL.	
	Examiner	Art Unit	
	RACHAEL E. WELTER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17 and 19-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/09, 8/3/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/09 has been entered.

Claim Status

Claims 15-17 and 19-25 are pending. Claims 1-14 and 18 are cancelled.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on May 15, 2009 and August 3, 2009 were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements were considered by the examiner. A signed copy of forms 1449 are enclosed herewith.

Withdrawn Rejection

The rejection of claim 18 rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and*

Practice of Pharmacy, 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (http://www.rxlist.com/actos-drug.htm) is withdrawn in light of applicant's cancellation of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 15-17, 19-21, 23, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and Practice of Pharmacy,* 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (http://www.rxlist.com/actos-drug.htm).

Piper teaches a pharmaceutical formulation which includes a combination of metformin and at least one other antidiabetic agent (pg. 6, lines 28-31), which can be a

thiazolidinedione (pg. 14, line 9), such as pioglitazone (pg. 15, line 20). As evidenced by Rx List, Takeda-Lilly-Actos (pg. 15, line 21) mentioned in Piper is a pioglitazone hydrochloride. Piper also teaches that the antidiabetic agent can be glyburide (pg. 8, lines 14-15). Furthermore, Piper teaches that the formulation has at least substantially equivalent efficacy in treating type 2 diabetes as compared to prior art antidiabetic formulations containing metformin, but with substantially reduced side effects (pg. 1, lines 10-14). In forming a low dose metformin hydrochloride and glyburide formulation, the granules are formed by wet granulation of a mixture of metformin and glyburide (pg. 23, lines 19-20). More specifically, Piper teaches that a dry mixture of croscarmellose sodium and glyburide were dispersed together followed by blending with the metformin hydrochloride/magnesium stearate in a high shear mixer with an aqueous povidone solution and dried. (pg. 26, lines 1-4). The dried granulation was reduced with a screening mill and mixed with microcrystalline cellulose using a tumble mixer (pg. 26, lines 8-10). Magnesium stearate was incorporated as a lubricant using a tumble mixer to produce the final compression blend (pg. 26, lines 10-12). The resultant blend was compressed into tablets and film-coated (pg. 26, lines 13-24). Because the granules are being formed from a mixture of metformin and glyburide and a high shear mixer is used, the reference implies that the biguanide and pioglitazone are uniformly dispersed. Furthermore, Piper teaches that the glyburide has a particle distribution of a 25% undersize value not more than 6 um, a 50% undersize value (also known as the mass median particle size) 7 to 10 um, and a 75% undersize value not more than 23 um (pg. 23, lines 11-15). Piper further conducted a study with particle size data to achieve

comparable bioavailability to Micronase (glyburide alone) from the combination product of glyburide and metformin (pg. 26, lines 24-29). According to Piper, the particle size values or particle distribution assured reproducibility of glyburide dissolution and bioavailability from metformin hydrochloride-glyburide tablets.

Piper does not explicitly teach a median particle size of biguanide (metformin) of 10-100 um or a ratio of median size biguanide particles to median size pioglitazone particles of 0.5 to 15.

However, according to Zhuang et al, a more uniform mixture is obtained by having a small particle size of each ingredient and a similar size of each ingredient (pg. 3, lines 4-5).

Therefore, given the teachings of Zhuang et al, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a similar biguanide median size to glyburide taught in Piper or its functional equivalent, pioglitzaone, resulting in a 1:1 ratio. One would have been motivated to do so in order to create a more consistent mixture during granulation because Zhuang et al suggest that similar sized ingredients make a more uniform mixture.

Furthermore, as evidenced by Remington and Piper, the particle size of a drug in an oral dosage form can affect its dissolution rates. According to Remington, higher dissolution rates may be achieved through the reduction of the particle size (pg. 675, column 1, "Effect of Particle Size On Dissolution"). Remington further teaches that in the case of cloramphenicol, formulations containing smaller particles (50-200 um) were absorbed faster than formulations containing larger particles (400-800 um). Moreover,

as taught in Piper, the particle sizes of glyburide were based on achieving a desired bioavailability. Thus, it is well known in the art and it would be obvious to an artisan of ordinary skill to optimize and manipulate the particle sizes based on the desired dissolution rates and bioavailability of the drug.

Regarding claim 21 and the coefficient of variation of the pioglitazone, the examiner has no access to laboratory equipment and burden is on applicant to prove that the reference teaches otherwise. When the reference discloses all the limitations of a claim except a property or function and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention, the examiner can shift the burden of proof to applicant as in *In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).*

Regarding claim 23, which is drawn to the dissolution rate of the formulation, this limitation is an intended use for the composition. Because it does not materially impact the structure of the composition itself, it is not given any patentable weight. Besides, the prior art teaches the obvious core structure of the solid formulation of metformin and pioglitazone, the formulation is capable of having the instantly claimed dissolution characteristics when subjected to the Paddle Method depending on the amounts of drug, drug solubility, and median particle size. Further, one of ordinary skill in the art would have been motivated to alter the dissolution characteristics of a drug formulation depending on the needs of a particular patient population.

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Piper (WO 01/32158) in view of Zhuang et al (*Practical Pharm. Prep. Tech.*, January 1999, p. 203-204) as evidenced by Remington (*Remington: The Science and Practice of Pharmacy*, 21st Edition, 2003, pp. 675-676) and RxList: The Internet Drug List (http://www.rxlist.com/actos-drug.htm) and further in view of *Remington (Remington's Pharmaceutical Sciences, 18th Edition, 1990, pg. 1639) and Kumar (US Patent No. 6,117,451).

*Note: The Remington 18th Edition will be referred to as RPS in the body of this rejection.

The disclosures of Piper and Zhuang et al were discussed above.

Piper and Zhuang et al do not explicitly teach solid preparations having a hardness of 100-400 N.

RPS teaches that the resistance of a tablet to chipping, abrasion or breakage under conditions of storage, transportation, and handling before usage depends on its hardness (column 1, "Tablet Hardness", lines 1-3). According to RPS, a hardness of 4 kg, which corresponds to approximately 40 N, is considered to be a minimum for a satisfactory tablet.

Kumar teaches a metformin hydrochloride formulation capable of being directly compressed with specific excipients having desired hardness, disintegrating ability, and acceptable dissolution characteristics (column 4, lines 65-67--column 5, lines 1-5). According to Kumar, microcrystalline cellulose is an excipient that is highly compressible and produces hard, strong tablets at a low machine pressure (column 9,

lines 18-20). Kumar further teaches that microcrystalline cellulose prevents chipping and capping of the metformin hydrochloride tablets (column 9, lines 20-21).

Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a tablet hardness of higher than 40 N. One would have been motivated to do so in order to make a satisfactory tablet that would be resistant to chipping, abrasion or breakage under certain conditions, as suggested by RPS.

Furthermore, as suggested by Kumar, it is known in the art to optimize and manipulate tablet hardness depending on a tablet's excipients and desired dissolution rate. Like Piper (see pg. 26, lines 8-10 of Piper), Kumar teaches microcrystalline cellulose as a preferred excipient and Kumar suggests a desired tablet hardness for metformin hydrochloride. Optimization of parameters is a routine practice that would be obvious to a person of ordinary skill in the art to employ and reasonably expect success. One would have been motivated to determine the optimal amount of each excipient in order to achieve the desired tablet hardness. See *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* & MPEP 2144.05. Burden is on the applicant to prove otherwise and show the criticality of the claimed hardness range.

Response to Arguments

Applicant's arguments filed 7/24/09 have been fully considered but they are not persuasive.

Applicant argues that the presently claimed preparations exhibit unexpected properties that make the presently claimed preparations suitable as an anti-diabetic

combination drug. Applicant submitted a Rule 132 Declaration demonstrating these unexpected results. According to applicant, the Declaration demonstrates that while equivalence can be achieved between pioglitazone in a combination drug and that in Actos (pioglitazone as the only active ingredient) in an in vitro dissolution test, bioequivalence of pioglitazone can only be achieved in a human body during clinical studies if the particles of the pioglitazone are micronized, specifically between 2-10 um as recited in instant claims 15 and 24. Applicant argues that such a discrepancy can be attributed to an unexpected in vivo drug interaction between the two active ingredients taking place in the human body, which is not only rare but also unpredictable to one of ordinary skill in the art. Applicant argues that the presently claimed invention provides a single-phase solid preparation, allowing the presently claimed preparation to be smaller in size, which at the same time allows both active ingredients to achieve bioequivalence. Applicant argues that even more surprisingly, the Declaration shows that the micronization of the pioglitazone particles did not significantly affect the uniformity of either of the active ingredients, contrary to the suggestion in the outstanding Office Action that one of ordinary skill in the art would have micronized pioglitazone for the purpose of increasing uniformity. Applicant argues that no combination of the cited references, Piper and/or Zhuang teaches or suggests that the lack of bioequivalence encountered when these drugs are combined could be overcome by a preparation featuring the selected combination of features recited in independent claims 15 and 24.

Applicant's Rule 132 Declaration is insufficient to overcome the rejection of the claims as set forth in the last Office action because:

Applicant has failed to show that a reduced particle size of 2-10 um of pioglitazone eliminated the discrepancies between the in vitro dissolution test and the clinical studies for both pioglitazone and metformin. In the Declaration, applicant contends that Examples 2, 3, 5, and 6 in the instant specification, which have a pioglitazone median size outside the claimed range do not achieve bioequivalence for both pioglitazone and metformin. Applicant shows these bioequivalence results in Table D1 of the Declaration. However, applicant merely states that when the particle size of pioglitazone is reduced in the present combination drug, bioequivalence for both pioglitazone and metformin can be achieved. Applicant has shown no dissolution profiles or data to show this unexpected result. As such, since applicant fails to show any objective evidence and merely states that a reduced particle size of pioglitazone of 2-10 um achieves bioequivalence for both pioglitazone and metformin, the Declaration appears as if it is an opinion Declaration. According to MPEP 716.01 (c), "Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application." In the instant case, the Declaration only provides conclusions without any probative value, i.e. evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, etc.

Additionally, the examiner notes that the limitation directed to the median ratio of the particle size in the instant claims is not critical to applicant's unexpected results.

The instant ratio of the particle sizes can be met without having pioglitazone with the instantly claimed particle size of 2-10 um and metformin with the particle size of 10-100 um.

Furthermore, the examiner notes that applicant's results are expected rather than unexpected in view of the prior art. Piper teaches that when glyburide is paired with metformin in a pharmaceutical formulation, the mass median particle size of glyburide is preferably 7-10 um (pg. 27, line 28) because this particle size assures reproducibility of glyburide dissolution and bioavailability from a metformin hydrochloride-glyburide tablet. Although the examiner notes that Piper paired glyburide and metformin in its examples, Piper also teaches that pioglitazone hydrochloride can be paired with metformin as an antidiabetic agent (pg. 15, line 20). As such, it is the position of the examiner that an artisan of ordinary skill would be motivated to pair metformin with piolgitazone hydrochloride in a tablet with a median particle size of pioglitazone in the claimed range (i.e., 7-10 um) in order to assure reproducibility of pioglitazone dissolution and bioavailability from a metformin hydrochloride-pioglitazone hydrochloride tablet. Therefore, applicant's unexpected results regarding the bioequivalence of metformin and pioglitazone are unpersuasive in light of Piper's teachings that a particle size of 7-10 um of an active ingredient paired with metformin can achieve comparable bioavailbility to itself from the combination product.

Conclusion

Claims 15-17 and 19-25 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
October 13, 2009